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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,362	01/19/2001	Solomon S. Steiner	PDC 119	8907

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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
08/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/766,362	STEINER ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-12,14-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12,14-18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Response, the Amendment and Applicant's Arguments/Remarks, all filed 05/16/08 is acknowledged.

Claims 1-5, 7-12, 14-18, 20 and 21 are pending in this action. Claims 1, 7 and 14 have been amended. Claims 6, 13 and19 have previously been cancelled. Claims 1-5, 7-12, 14-18, 20 and 21 remain rejected.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (hereafter "Steiner") (US Pat. No. 5,503,852).

Steiner *et al.* ('852) teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and Abstract.

According to Steiner, biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner *et al*. teach a system based upon diketopiperazine or one of its substitution derivatives, including *diketomorpholines and diketodioxanes*. The diketopiperazine synthetic intermediates are preferably formed by cyclodimerization to form diketopiperazine derivatives at elevated temperatures under dehydrating conditions, functionalized on the side chains, and then precipitated with drug to be incorporated into microparticles (see abstract; col. 4, lines 49-67; col. 7, lines 8-11).

The protective material, the diketopiperazines, are not biologically active and do not alter the pharmacologic properties of the therapeutic agents (col. 11, lines 1-3).

The instant invention is drawn to a composition for the nasal administration of a drug in dry powder form for administration to the nasal region, whereby the dry powder comprises microparticles having a particle size of 10 to 20 microns and comprising drug and a diketopiperazine. There is no significant patentable distinction observed between the instant invention and the prior art since the prior art teaches drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are between 0.1 to 10 microns in diameter and are used for nasal applications. Steiner explicitly teaches that their microparticles can be between 0.1 and 10 microns. Thus, the '10 micron' size microparticles disclosed by Steiner overlaps with the "10 microns" claimed herein by Applicant and hence the "10 microns" of Steiner satisfies the

claim limitation requirement of "10 to 20 microns". The 10 microns taught by the prior art is an overlapping particle size that falls within the range of "10 to 20 microns" instantly claimed and thus reads on the instant particle size limitations. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). In this case, Applicants have not established that their claimed range provides for unexpected results over the ranges disclosed by the art.

Furthermore, Applicants have not demonstrated that the "10 micron" size range claimed is a critical lower limit. This is evidenced by Applicant's own specification. For instance, formulations I and II on pages 13 and 14 demonstrate particles with micron sizes that are less than 10 microns. More specifically, formulation I on p. 13 demonstrates that 10% of particles had a particle size of only *3.15* microns. Similarly, Formulation II on page 14 demonstrates that 10% of particles had a particle size of only *2.99* microns. Therefore, this clearly establishes that the 'between 10 microns' claimed by Applicants is not a critical lower maximum particle size limitation. The determination of a suitable or effective particle size is within the level of one of ordinary skill in the art, based on routine experimentation. In this instance, one of ordinary skill in the art would have been motivated to nasally administer the microparticles of Steiner that comprise a drug and diketopiperazine and further optimize, if necessary, the particle size or size range for the intended application (i.e., nasal applications). One would be motivated to do this with a reasonable expectation of success of obtaining an enhanced drug delivery system that effectively (nasally) administers the microparticles in the (nasal) cavity for maximum treatment. It is the position of the Examiner that the 10-micron size microparticles of Steiner would be

retained in the mucosal cavity for sufficient drug delivery and thus, would be suitable for their intended purpose. Absent a showing of evidence to the contrary, Steiner's microparticles would be suitable for nasal administration. Hence, the instant invention, given the explicit teachings of Steiner delineated above, would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Claims 3, 8, 10, 16, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (US Pat. No. 5,503,852) as applied to claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 above and further in view of Illum (US Pat. No. 5,690,954).

Steiner *et al.* ('852), as delineated above, teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract.

According to Steiner, biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner does not explicitly teach the selective antihistamines chosen from chlorpheniramine and azelastine.

Illum ('954) teaches a drug delivery system for nasal administration of an active drug in dry powder form wherein the drug delivery system comprises microsphere particles formed of active drugs that include *antihistamines*, vasoconstrictors, anti-inflammatory agents and anesthetics whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 5, line 14 through col. 6, line 53); (col. 9, lines 24-61). (The range of about 10 microns to about 100 microns taught by Illum encompasses the range of "10 to 20 microns" claimed by Applicant).

Suitable active drugs disclosed are anti-inflammatory agents, vasoconstrictors, anesthetics (analgesics) and antihistaminic agents. Antihistaminic agents are diphenhydramine hydrochloride, *chloropheniramine maleate* and clemastine. The microspheres are administered via the nasal route using a nasal insufflator device. Examples of these are already employed for commercial powder systems intended for nasal application (*e.g.*, Fisons Lomudal System); (col. 8, line 44 through col. 9, line 60).

Illum teaches that the drug to be administered to a mucosal surface such as the nose, eye, etc., can be administered as a powder and can also be administered in the form of a colloidal particle comprising a microsphere system (col. 5, line 14-26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the antihistamines (*i.e.*, chlorpheniramine) as taught by Illum within the microparticulate formulations of Steiner. One would be motivated to do so with a reasonable expectation of success because Illum teaches a nasally administered drug delivery system and device comprising active agents that include antistamines, such as those claimed, as

well as vasoconstrictors and anesthetics (analgesics), which are effective active agents for their formulation and teach that the drugs are used for nasal administration provided in a dry powder form. The expected result would be an improved and effective microparticulate drug delivery system for nasal administration, as also desired by Applicant.

Pertinent Art

Prior Art made of record and deemed relevant by Examiner:

U.S. Patent No. 6,136,835 Camden 10/2000

Response to Arguments

Applicant's arguments filed 05/16/08 have been fully considered but were not found to be persuasive.

- **Rejection under 35 U.S.C. §103(a) of claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 over Steiner et al. (US Pat. No. 5,503,852) and Rejection under 35 U.S.C. §103(a) of claims 3, 8, 10, 16, 20 and 21 over Steiner et al. (USPN 5,503,852) in view of Illum (USPN 5,690,954):**

Applicant argued, "Steiner discloses particles between 0.1 to 10 microns in diameter. Steiner does not disclose microparticles wherein more than 50% of the microparticles have a particles size greater than about 10 microns. The microparticles of Steiner are primarily used for delivery to the pulmonary system, a use requiring smaller particles. Illum states that their particles should be a size of between 10 and 100 microns. The majority of the microspheres produced by Illum are greater than 20 microns in size. While there is overlap in the range of the

claimed microparticles and the microspheres of Illum, Illum does not teach or suggest microparticles between about 10 microns and about 20 microns in diameter wherein more than 50% of the microparticles have a particles size greater than about 10 microns."

These arguments have been fully considered but were not found to be persuasive. The Examiner incorporates the previous arguments presented in the previous office action and adds the additional statements for clarification. A thorough and reasonable reading of applicant's specification indicate that the average size of the particles in the dry powder **should be between about 10 and about 20 microns, etc.**. The specification, including the examples do not establish the criticality of the minimum lower limit urged by Applicant in the response. The fact that the art uses the same drug in the same form for the same purpose is more compelling that it would be *prima facie* obvious to one of ordinary skill in this art to select, through routine experimentation suitable micron sizes. Applicant's background of the invention states 'approximately and between about'. This language does not suggest the exactness of size argued by Applicant. Arguments that more will be delivered to the nasal area are not persuasive since product claims do not contain specific amounts of drug, and the process is silent regarding the amount of drug to be delivered. Nothing in the specification establishes an unexpected or non-obvious amount of drug delivery. Applicant has not demonstrated by a presentation of data that the particle sizes of the references are not effective in the results desired by Applicant, i.e., reduced drug amounts to result in the same therapeutic treatment. But in any event, these amounts are not claimed. When dealing with claims to approximate sizes, with limitations on the percentages of particles permitted, Applicant has the burden of establishing some unusual and/or unexpected result over the cited art. Applicant presents no data establishing that the 50% particle

size limitation would be an improved result over the presence of the smaller micron-sized averaged particles of the art.

The rejections of record have been maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley, can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/

Primary Examiner, Art Unit 1618

hns

August 15, 2008